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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

***21* CFR Part 314**

[Docket No. 94N–0449]

RIN 091 O-AA78

New Drug Applications; Drug Master Files

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising its regulation governing drug master files (DMF's). FDA is removing the provision for submitting Type I DMF's and will no longer permit information subrnitted in a Type I DMF to be incorporated by reference in investigational new drug applications (IND's), new drug applications (NDA's), abbreviated new drug applications (ANDA's), or amendments or supplements to any of these. This rule is intended to eliminate submissions of information that are not necessary either to conduct inspections of manufacturing facilities or to review the chemistry, manufacturing, and controls sections of IND's, NDA's, and abbreviated applications.

EFFECTIVE DATE: ***(Insert date 180 days after date of publication in the* Federal Register.)**

FOR FURTHER INFORMATION CONTACT:

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. Robert A. Yetter, Center for Biologics Evaluation and Research (HFM–10), Food and Drug

Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-0373.

SUPPLEMENTARY INFORMATION:

I. Background

A DMF is a voluntary submission to FDA that may be used to provide confidential, detailed information about the facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drug products. The regulations in 21 CFR 314.420(a) describe five types of DMF's according to the kind of information to be submitted. Type I submissions include manufacturing site, facilities, operating procedures, and personnel information. Type II submissions include information regarding drug substances, drug substance intermediates, and materials used to prepare them, or drug products. Type III submissions include information about packaging materials. Type IV submissions include information concerning excipients, colorants, flavors, essences, or materials used in their preparation. Type V submissions, detailed in the guidance for industry entitled "Drug Master Files" (September 1, 1989), include FDA-accepted reference information. DMF's allow regulated industry to submit to FDA information that may be used to support an IND, NDA, ANDA, another DMF, an export application, or amendments or supplements to any of these. DMF information may be incorporated by reference into a drug application or supplement without public disclosure.

FDA intended to use information submitted in a Type I DMF to plan its on-site inspections of and travel to foreign drug manufacturing facilities. In December 1992, the Chemistry, Manufacturing, and Controls Coordinating Committee (CMCCC) of the Center for Drug Evaluation and Research (CDER) established a DMF task force to review DMF procedures and consider ways of improving the DMF system. One of the task force recommendations was that Type I DMF's be eliminated. The recommendation was based on a number of factors:

1. The information contained in Type I DMF's was often outdated.

2. The Type I DMF was not always easily accessible to FDA investigators.

3. The review divisions in CDER do not review the information in most Type I DMF's. Although information from Type I DMF's has often been incorporated by reference into IND's, NDA's, and abbreviated applications, the information is not required for review of the chemistry, manufacturing, and controls section of an application. Under 21 CFR 314.50(d)(l)(i) and (d)(1)(ii), a drug product applicant is required to furnish in the application the name and location of facilities used in the manufacture of the drug substance or drug product.

4. Information concerning the facility is maintained onsite where it is available for the investigator.

The CMCCC adopted the recommendation of the DMF Task Force and, subsequently, FDA proposed eliminating Type I DMF's in the **Federal Register** of July 3, 1995 (60 FR 34486). FDA also proposed to implement a procedure by which DMF holders could request that certain information currently contained in Type I DMF's be transferred to Types II through V.

FDA is finalizing its proposal to eliminate Type I DMF's. In so doing, the agency will no longer accept Type I DMF's or correspondence updating existing Type I DMF's and will no longer permit information previously submitted in a Type I DMF to be incorporated by reference in IND's, NDA's, ANDA's, and supplemental applications for drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355).

The Center for Biologics Evaluation and Research (CBER) has used Type I Master Files in a manner different from that used by CDER. Certain biological products, such as gene therapy products, require review of some facility information to assess their safety for use in clinical trials under IND. CBER will accept facility information for such products in Type V Master Files. CBER intends to issue a guidance-on the information that may be submitted in a Type V Master File without previously obtaining permission.

II. Comments on the Proposed Rule

The agency received seven comments on the proposed rule and several of these raised multiple issues. A number of comments expressed general support for the proposal. A summary of the comments and the agency's responses follows.

1. One firm stated that it will be manufacturing drug products for other U.S. and non-U.S. companies and needs a means to submit confidential, technical information to FDA (e.g., information regarding the firm's new manufacturing facility, including, but not limited to, air handling systems, milling, blending, and filling technology). The firm emphasized that if Type I DMF's are eliminated, confidential information regarding the facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of drugs for human use would not be available for referencing by sponsors of IND's or NDA's with which the firm will contract. In addition, FDA's review divisions will not be able to rely on the applications themselves for information typically included in a Type I DMF. The fii noted that without a Type I DMF, a Type II DMF (intermediates, drug substances, and drug products) might be the only alternative for supplying the agency with certain information and that it would be forced to file a Type II DMF for each company for which it does drug product manufacturing. The firm also stated that the submission of multiple Type II DMF's instead of a single Type I would place an unnecessary paper burden on the agency. The firm further noted that if the agency relies on preapproval inspections, it faces the possibility of multiple inspections in any given year, placing unnecessary burdens on valuable FDA resources (i.e., multiple inspections of the same facility).

One comment noted that it is irrelevant that field investigators do not use Type I DMF's and that, since Type I submissions are voluntary, the agency should continue to allow firms the convenience of referencing Type I submissions. Another comment suggested that instead of FDA eliminating Type I DMF's, industry should be required to keep the information current. The comment stated that the privilege of incorporating Type I DMF information by reference should be denied on a case-by-case basis to those firms that do not keep information current.

The agency believes that several of these comments are based on a misunderstanding of the agency's reliance on information contained in Type I DMF's during the drug application review process. Information contained in Type I DMF's is not reviewed by CDER reviewers, and it plays no role in processing a drug product application.

The Type I DMF was intended to assist FDA in conducting onsite inspections of foreign manufacturing facilities. As noted above, the agency determined that the Type I DMF was not always easily accessible to investigators and that information in the document was often out-of-date. The drug product application is required to provide information on the location of manufacturing facilities and it is this current, product-specific information that is used by CDER review divisions. Continuing to maintain Type I DMF's when the information is not used by the agency provides no benefit to either regulated industry or the agency.

If a firm is performing different processing steps for a customer, a Type I DMF would not provide the information necessary for adequate review. Moreover, the elimination of Type I DMF's does not mean that a firm would be required to file a Type II DMF for each company for which it manufactures drug products. Reviewers examine the details of the manufacturing process as they apply to each individual product and procedures used in the manufacture of more than one drug product may be included in the same Type II DMF.

Concerns about a possible strain on FDA resources because of multiple inspections are not relevant to the Type I DMF issue since inspections are conducted in accordance with current agency inspection policy, which applies whether or not a firm has a Type I DMF. The current agency policy on inspections is described in the agency's Investigations Operations Manual. Prior to the approval of a drug product, the facility that will manufacture the product will generally be inspected by FDA unless there has been a recent inspection for other reasons.

2. One comment stated that the production of "Generic Compounds" (which could conceivably be manufactured in smaller, stand-alone facilities possibly located in remote areas) is generally not adequately described in drug product applications and other written material

submitted to IDA. The comment stated that such inadequate descriptions could increase the risk of problems resulting from admixing imported products that may not have been manufactured in a facility for which a DMF has been filed. The comment noted that a full description of a facility enhances FDA's ability to identify facilities that do not meet FDA criteria.

CDER believes that a current, accurate facility description at the manufacturing site and an inspection of the facility are the best sources of information for assessing a facility's ability to meet FDA standards. Current, accurate information is particularly important when a facility is remote.

3. One comment noted that agency investigators of foreign manufacturers had stated that the Type I DMF was of immense value because of the information provided. The comment noted that "having more information was preferable to having none," and that the Type I format was superior in providing that information.

The agency agrees that accurate manufacturing information is important in evaluating drug product applications and preparing for inspections. FDA does not agree, for reasons explained above and in the proposed rule, that the Type I DMF is the most effective method of providing this information.

4. One comment stated that the proposed rule should be reconsidered because it is not globally oriented. The comment stated that., at the present time, several foreign governments link approval and acceptance of U.S. products to the data listed in Type I DMF's.

It is not clear from the comment how foreign governments link approval and acceptance of U.S. products to the data listed in Type I DMF's since these data are not reviewed in the approval process for U.S. products. Foreign governments that have previously relied on the information in a Type I DMF can request that the firm provide a description of the manufacturing facility to them.

5. One comment asserted that switching information from one type of DMF to another would not result in a reduction in paperwork, because there would be no basic change in the system.

The comment suggested that a proposal to prompt industry to withdraw inactive Type I Master Files might be more appropriate. The comment observed that there would be a reduction in paperwork if the amount of information incorporated in a Type I DMF were limited to that specified in the proposed rule as appropriate for transfer to a Type V DMF. Another comment observed that the elimination of Type I DMF's will increase the paperwork burden for industry if information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs can no longer be reported in a Type I DMF and incorporated by reference.

Because FDA investigators and CDER review divisions do not rely on information in a Type I DMF document for inspection or approval purposes, the agency finds that the mere withdrawal of inactive Type I DMF's would not address the agency's concern that the Type I DMF is an inadequate vehicle for information. To address this concern, the agency is eliminating the production and maintenance of all Type I DMF documents. Therefore, based on FDA's experience, the agency concludes that it is reasonable to anticipate a reduction in the paperwork burden by eliminating the requirement that industry produce and maintain the Type I DMF document.

6. One comment asserted that the proposal would require a rewrite of the current guidance to provide industry with information regarding the format and content of the Type V DMF's. The agency notes that the guidance for industry on DMF's is currently undergoing revision and any changes regarding Type V DMF's will require no significant additional resources. The agency advises that the only Type I DMF's that may be converted to Type V's are those covering sterile processing facilities and other special cases. As detailed in the discussion on implementation below, these will be examined on a case-by-case basis to decide if transferring them is justified. The agency does not anticipate that substantial agency resources will be required to evaluate requests for the transfer of information currently included in Type I DMF's to Types II, III, IV, or V DMF's.

III. Implementation of the Rule

7. One comment suggested that the proposed implementation date of 60 days after publication should be reconsidered because this timeframe does not permit adequate time to revise operating procedures. One comment suggested that the proposed rule should be implemented in conjunction with an educational effort, including a workshop on DMF's and publicity to prepare those affected by the new requirements. One comment asserted that the transfer of information from a Type I DMF to another type would require a review of written requests by the DMF staff and that this could result in a significant economic impact on the agency. One comment asserted that the proposed rule did not address those current applications which reference Type I DMF's.

Based on comments and FDA's own evaluation, the agency has concluded that the proposed implementation period is inadequate, particularly for foreign firms seeking approval where Type I DMF's were referenced. Some firms will need time to develop alternative procedures. The agency has determined that the effective date will be 180 days after the date of publication of the final rule in the **Federal Register**.

After the effective date of the rule, the agency will no longer accept new Type I DMF's or correspondence updating existing Type I DMF's. Type I DMF's will be transferred to the Federal Records Center and the information in Type I DMF's currently on file may no longer be incorporated by reference into new applications, amendments, or supplements. These changes will supersede all information regarding Type I DMF's detailed in the current guidance for industry on DMF's.

To accommodate firms that have submitted information under a Type I DMF that should have been filed under DMF Types II through V, a list of all CDER Type I DMF's is available for public review in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, under the docket number found in brackets in the heading of this document. The list is also available on the CDER Internet site at http://www.fda.gov/cder/dmf/index.htm. If a DMF holder believes that its Type I DMF should be

recategorized or transferred to another type of DMF, the DMF holder may contact the Drug Master File Staff within 180 days of publication of this rule in the **Federal Register** [1]. FDA will consider recategorizing an entire Type I DMF to another type only if the Type I DMF contains substantive information other than information concerning manufacturing site, facilities, operating procedures, and personnel.

Some Type I DMF's currently on file contain information concerning sterilization process validation and other information relevant to the review, evaluation, and assurance of the sterility of sterile products. For sterile items that are not the subject of an IND, NDA, or ANDA and that are sold to a second party (e.g., rubber closures that are sterilized by the manufacturer and sold to a second party), CDER will consider transferring product-specific and general information concerning sterilization process validation to the DMF file or DMF type (i.e., II through IV) under which manufacturing information for the specific item is filed. For instance, DMF's concerned with sterilization procedures for rubber stoppers would be reclassified as Type III DMF's (packaging materials). Contract manufacturers of sterile drug substances and sterile finished drug products including biotechnology products filed as DMF's, contract sterilization firms (e.g., ethylene oxide, gamma radiation, and electron beam radiation), and manufacturers of sterile finished drug products that are the subject of a drug product application may request a transfer from Type I to Type V DMF of nonproduct-specific information and procedures that are submitted to support a claim of sterility. Where applicable, the content and format of such transferred information should follow FDA's guidance for industry entitled "Submission of Documentation for Sterilization Process Validation Applications for Human and Veterinary Drug Products" (November 1, 1994).

CBER intends to administratively recategorize current Type I Master Files that are still needed to other Master File Types as appropriate. CBER will make a list of those Type I Master Files that have not been recategorized available for public review in the Dockets Management Branch

[1] Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852. The Drug Master File Staff may also be reached at 301432742 10 or at DMFType 1 @cder.fda.gov.

(address'above), under the docket number found in brackets in the heading of this document, no later than 30 days after date of publication of this document in the **Federal Register**. The list will also be available on the CBER Internet site at www.fda.gov/CBER. If a holder of a Type I Master File believes that the Master File should be recategorized, the holder may contact the Division of Manufacturing and Product Quality (DMPQ) (HFM–207), Office of Compliance and Biologics Quality, CBER, 1401 Rockville Pike, Rockville, MD 20852-1448. DMPQ may also be reached at 301-827-3031.

The agency advises that applicants who have current approved applications that reference Type I DMF's transferred to Type V DMF's may notify the agency of this change in an annual report as provided in 2 1 CFR 3 14.70.

FDA has examined the possible impact of these changes and believes that a review of requests to transfer DMF's can be handled without placing a significant burden on the agency.

The agency agrees with the suggestion that the final rule should be implemented in conjunction with an educational effort and will work with the press and industry trade associations to publicize the obligations and options provided by the regulation. Based on industry response and requests for further information, FDA will determine whether to provide further educational opportunities such as workshops.

IV. Environmental Impact

The agency has determined under 21 CFR 2$.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule will lessen paperwork and recordkeeping burdens and impose no significant new burdens, the agency certifies that the regulation will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The Unfunded Mandates Reform Act (Public Law 104–4) requires that agencies prepare a written statement including an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more. This final rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of $100 million or more.

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a Federalism summary impact statement is not required.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13 132. FDA has determined that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 314 is amended as follows:

PART 314-APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321,331, 351, 352, 353, 355,371, 374, 379e.

2. Section 314.420 is amended by removing and reserving paragraph (a)(l) and by revising the second sentence of paragraph (a)(5) to read as follows:

§ 314.420 Drug master files.

(a) * * *

(1) [Reserved]

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(5) * * * (A person wishing to submit information and supporting data in a drug master file (DMF) that is not covered by Types II through IV DMF's must first submit a letter of intent to the Drug Master File Staff, Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852. * * *

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Dated: 9/1/99
September 1, 1999

Margaret M. Dotzel
Acting Associate Commissioner for Policy

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